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AMENDMENT UNDER 37 C.F.R. §1.116
EXPEDITED PROSECUTION
ART UNIT 1632

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Merton Bernfield and Ofer Reizes

Serial No: 08/965,356 Art Unit: 1632

Filed: November 6, 1999 Examiner: A. Baker

For: METHODS AND REAGENTS FOR REGULATING OBESITY

BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE

Sir:

The enclosed materials and following remarks are in response to the Office Action mailed February 1, 2000. A Petition for an Extension of Time for two months, up to and including July 1, 2000, and the appropriate fee for a small entity are also enclosed.

Claims 1, 3-6, 10 and 12-15 were rejected under 35 U.S.C. §112, first paragraph, on the basis that the application is enabling solely for a transgenic mouse comprising a stably integrated DNA sequence encoding a syndecan operably linked to a promoter, where expression of the DNA sequence results in the mouse developing maturity onset obesity and methods of using these mice. This rejection is respectfully traversed.

As discussed in the interview, it is the opinion of the inventors, *who are skilled in the field of obesity and of transgenic rodents*, that studies done to make and screen compounds using

genetically engineered mice are predictable of the same results in rats. Enclosed in support thereof are copies of articles that demonstrate that results obtained with mice are predictive of results obtained with rats.

1. An identical methodology is used to generate transgenic mice and rats.

The literature makes clear that identical methods are utilized in the production of transgenic mice and rats. See DNX transgenic sciences fact sheet, Charles River Laboratories Transgenic Animal Science: Principles and Methods, and Homone Res (1992):37 (suppl 3): 74-87 the Growth Hormone Transgenic Mouse as an Experimental Model for Growth Research: Clinical and pathological Studies. Because identical methods are used in the generation of transgenic mice and rats, there would be no technical barriers in the use of the mice findings in rats.

2. Identical phenotypes result from transgenic expression of heterologous genes in the hypothalamus of rats and mice.

Growth Hormone (GH) overexpression in mice and rats are obese and diabetic.

Transgenic mice and rats have been useful in defining a role for GH in development and energy homeostasis. These studies indicate that GH is responsive to physiological stimuli and is released in a pulsatile manner. When human GH is introduced transgenically into mice or rats in an unregulated manner, the results are identical, resulting in acromegaly, obesity and diabetes. Because transgenic expression of a heterologous gene in the hypothalamus gives rise to identical phenotypes in mice and rats, the data from transgenic mice expressing the syndecan could be easily extrapolated to rats. See Bartke, A., et al., Effects of growth hormone overexpression and growth hormone resistance on neuroendocrine and reproductive functions in transgenic and knock-out mice. Proc. Soc. Exp. Biol. Med. 222: 113-123, (1999), and Ideda, A., et al., Obesity

and insulin resistance in human growth hormone transgenic rats. Endocrinology 139: 3057-3063. (1998).

3. Use of the CMV promoter leads to expression of heterologous genes in the same hypothalamic nuclei in mice and rats.

The CMV promoter expresses the syndecan-1 transgene in the mouse hypothalamus, specifically, in the arcuate, paraventricular, supraoptic, suprachiasmatic, dorsomedial and lateral area nuclei. Similarly in the rat, the CMV promoter expresses the kallikrein transgene in identical hypothalamic nuclei when introduced into the third ventricle. Because the same promoter dictates the near identical expression pattern in mice and rats, one would predict the same results in rats as in the transgenic mice. See, Wang, C., et al. Central delivery of human tissue kallikrein gene reduces blood pressure in hypertensive rats. BBRC 244: 449-454. (1998).

4. Identical hypothalamic mechanisms of obesity exist in mice and rats.

Classical mutations show identical obese phenotypes in mice and rats.

Leptin, a circulating hormone synthesized and secreted by adipocytes, notifies the hypothalamus/brain of the overall level of the body's energy stores. The leptin receptor, a hypothalamically expressed transmembrane signaling protein involved in sensing and responding to circulating levels of leptin, is the *ob* (obese) gene product. Mutations in the leptin receptor in both mice (*db/db*) and rats (Zucker *fatty*) cause early onset obesity in an identical physiological manner.

Hypothalamic lesions give rise to identical obesity syndromes in mice and rats.

Based on numerous studies involving surgical lesions in mice and rats, the ventromedial, dorsomedial and lateral areas of the hypothalamus are implicated as centers for regulating energy homeostasis. The identical phenotypes are likely due to the identical localization of signaling

pathways involved in energy balance in mice and rats. These include the leptin receptor, as well as other neuropeptides and their receptors involved in energy balance, such as neuropeptide Y (NPY) -melanocyte stimulating hormone (MSH), agouti-related protein (Agrp), orexins, melanin concentrating hormone (MCH), and corcicotropin releasing hormone (CRH). Because perturbation of all known hypothalamic signaling cascades in either mice or rats has the same outcome on obesity, results in rats are predictable based on the transgenic mouse data. See, Spiegelman, B.M., et al. Adipogenesis and obesity: rounding out the big picture. Cell 87: 377-389 (1996), Flier, J.S., et al. Obesity and the hypothalamus: novel peptides for new pathways. Cell 92: 437-440 (1998), and Augustin, K.A., et al. Rodent mutant models of obesity and their correlations to human obesity. The Anatomical Record 257: 64-72 (1999).

In summary, the more relevant literature discussed above fully supports that the methods and reagents for making rats using the same methods and reagents as in mice are enabled and predictable, and that the results, i.e., a transgenic animal expressing the syndecan which is characterized by an obese phenotype predictable.

Allowance of all claims 1, 3-6, 10, 12-15 is earnestly solicited. All claims as currently pending are attached in an appendix for the convenience of the examiner.

Respectfully submitted,

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CERTIFICATE OF HAND DELIVERY (37 CFR 1.6)

I hereby certify that this Response, along with any paper referred to as being attached or enclosed, is being hand delivered on the date shown below to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: June 8, 2000

Patrea L. Pabst